726: Safety and Efficacy of Six Months´ Open Label Extension Post-RCT Using the Novel Cathepsin K Inhibitor MIV-711 in Patients with Osteoarthritis

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Background and Aim

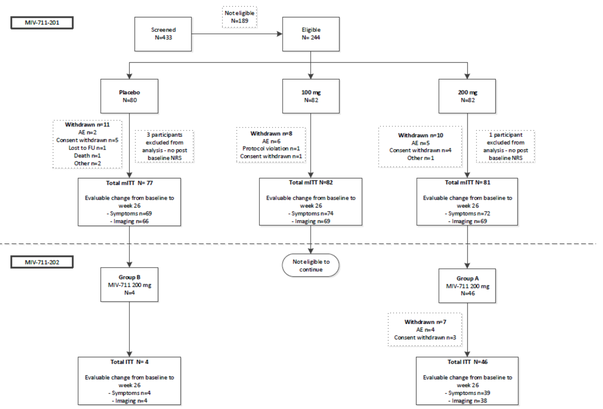
- Osteoarthritis (OA) is one of the fastest growing chronic conditions worldwide.
- Current treatments available for OA are aimed at controlling pain. There is a need for new therapies, so called Disease Modifying Osteoarthritis Drugs (DMOADs) that can prevent joint structural degeneration.
- MIV-711, a cathepsin K inhibitor, demonstrated effects versus placebo on both joint bone area and cartilage thickness following 6 months´ treatment (MIV-711-201 study presented at OARSI 2018, abstract 29).
- The aim of this study was to assess safety and efficacy measures in a subset of patients that had been included in the placebo-controlled study. All enrolled patients received six months of open-label treatment with MIV-711.

Methods

MIV-711-202 Study design

- MIV-711-201 was the initial randomized, controlled, multicentre, 3 arm, Phase II study
- Patients were eligible for enrollment in the current MIV-711-202 extension study if they were previously enrolled in the initial placebo-controlled study and had received either
  1) MIV-711 200 mg and had no clinical worsening of knee pain symptoms **(Group A)**, assessed on the Numeric Rating Scale (NRS) at the end of treatment (ΔNRS≤2) or
  2) placebo and had clinical worsening of knee pain symptoms **(Group B)** at the end of treatment assessed on the NRS (ΔNRS≥2).
- All patients in the extension study received MIV-711 200 mg once daily.
- Patients, staff and Sponsor were blinded to the prior treatment allocation in the placebo-controlled MIV-711-201 study.
- The patients remained on their usual analgesic regimen throughout the two studies.
- The placebo-controlled study employed a K-L 2 or 3 selection method based on local radiologist assessment, with the exclusion of K-L 0 and 4 as assessed by a central reader.
- Primary outcome was safety, with MRI measures as secondary outcomes and symptom and biomarker measures were assessed as exploratory outcomes.

Patient study flow chart



Patient Details

		MIV-711-201		MIV-711-202		
		200 mg	Overall	Group A	Group B	Overall
	n	81	240	46	4	50
Age (years)	Mean	62.0	61.8	61.5	65.5	61.8
BMI (kg/m^2)	Mean	32.0	32.2	31.9	29.5	31.7
Female	NA	58 (71.6%)	184 (76.7%)	31 (67.4%)	3 (75%)	34 (68.0%)
Discontinuations	NA	10	29	7	0	7

- Out of the 215 patients completing the placebo-controlled study, 50 patients were enrolled in the extension study.
- Overall demographics in the extension study were similar to the placebo-controlled study.
- In this poster, for clarity and given the relative size of the groups, efficacy data is only presented for Group A (patients continuing with 200 mg MIV-711 in the extension study).

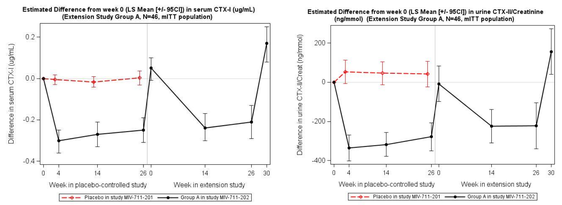
Safety and Tolerability

	MIV-711-201	MIV-711-201*			MIV-711-202		
	200 mg MIV-711 N = 82	Group A 26 weeks N = 46	Group B 26 weeks N = 4	Overall N = 50	Group A 26 weeks N = 46	Group B 26 weeks N = 4	Overall N = 50
	nn (%) E	nn (%) E	nn (%) E	nn (%) E	nn (%) E	nn (%) E	nn (%) E
All TEAEs	43 (52.4%) 118	22 (47.8%) 54	2 (50.0%) 5	24 (48.0%) 59	21 (45.7%) 50	2 (50.0%) 2	23 (46.0%) 52
Related* TEAEs	20 (24.4%) 37	8 (17.4%) 13	0	8 (16.0%) 13	1 (2.2%) 4	0	1 (2.0%) 4
Mild TEAEs	17 (20.7%) 57	8 (17.4%) 25	0	8 (16.0%) 25	6 (13.0%) 12	1 (25.0%) 1	7 (14.0%) 13
Moderate TEAEs	21 (25.6%) 55	11 (23.9%) 26	2 (50.0%) 5	13 (26.0%) 31	14 (30.4%) 34	1 (25.0%) 1	15 (30.0%) 35
Severe TEAEs	5 (6.1%) 6	3 (6.5%) 3	0	3 (6.0%) 3	1 (2.2%) 5	0	1 (2.0%) 5
Deaths	0	0	0	0	0	0	0
Serious TEAEs	2 (2.4%) 2	1 (2.2%) 1	0	1 (2.0%) 1	2 (4.3%) 10	0	2 (4.0%) 10
TEAEs Leading to Early Discontinuation from Study	4 (4.9%) 10	NA	NA	NA	4 (8.7%) 7	0	4 (8.0%) 7

*Numbers for Study MIV-711-201 are for subjects who continued into Study MIV-711-202 only

- MIV-711 showed acceptable tolerability; overall frequency of Treatment Emergent Adverse Effects (TEAEs) was similar to that seen in the placebo-controlled study.
- A Data Monitoring Committee recommended study to proceed without modification at the two preplanned safety reviews.
- Skin (morphea) and cardiovascular events were considered Adverse Events of Special Interest (AESIs) due to prior Cathepsin K inhibitor programs.
- No cases of morphea/scleroderma and only one TEAE in the SOC of skin disorders (psoriasis) were reported in the extension study.
- The frequency of cardiovascular events was judged to be within the expected range for an elderly, demographically challenged population but cardiovascular monitoring should still be considered in future studies.

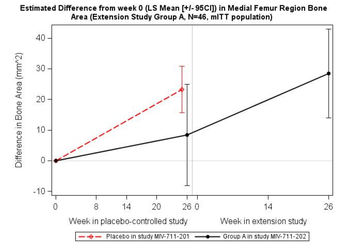
Effect of MIV-711 on Biomarkers: CTX-I and CTX-II



The figures cover the change in Group A (n=46) in both the initial placebo-controlled study and the subsequent extension study.

- CTX-I and CTX-II were supressed compared to baseline throughout the 12-month treatment period, except during the transitional inter-trial treatment interruption (approximately 10-15 days' duration)

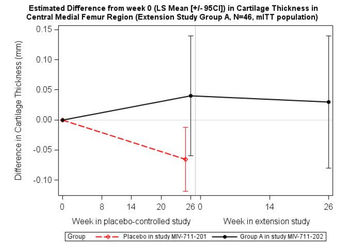
Effect of MIV-711 on Joint Structure: Bone Area



The figure covers the change in Group A (n=46) in both the initial placebo-controlled study and the subsequent extension study.

- The growth in medial femur bone area was reduced compared with the historical control (placebo group in the main study) with an LS Mean increase of 28.4 mm^2 [95%CI 13.9, 43.0] after 12 months´ treatment with MIV-711 compared with 23.2 mm^2 [95%CI 15.7, 30.9] after six months´ with placebo.

Effect of MIV-711 on Joint Structure: Cartilage Loss



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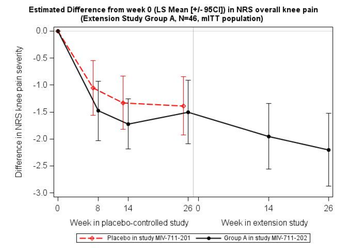
- The increase in thickness of the femoral joint cartilage was 0.03 mm [95%CI -0.08, 0.14] at the end of the 12-month period compared to a decrease of 0.07 mm [95%CI -0.12, -0.01] after six months´ with placebo.

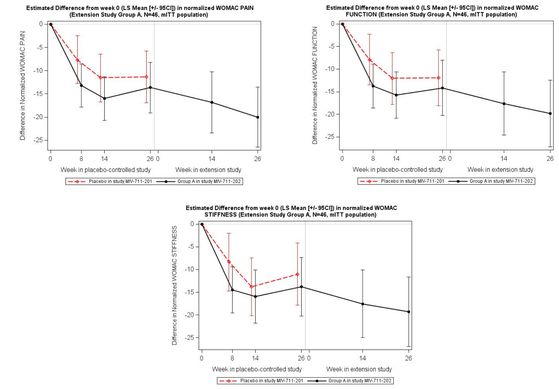
Effect of MIV-711 on Symptoms: NRS average Pain



The figures cover the change in Group A (n=46) in both the initial placebo-controlled study and the subsequent extension study.

- The effect on NRS average knee pain was maintained in the extension study.

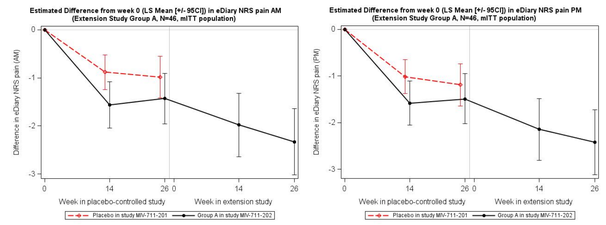
Effects of MIV-711 on Symptoms: WOMAC



The figures cover the change in Group A (n=46) in both the initial placebo-controlled study and the subsequent extension study.

- The normalized WOMAC scores (pain, function and stiffness) all had a continuing decline over the 12 months´ of treatment with MIV-711.

Effect of MIV-711 on Symptoms: e-diary assessed NRS



The figures cover the change in Group A (n=46) in both the initial placebo-controlled study and the subsequent extension study.

- E-diary NRS pain scores had a similar decline as to the NRS average pain scores over the 12-month period.

Discussion and Conclusions

- This study demonstrated that MIV-711 has acceptable safety and tolerability in knee OA patients, with the overall safety profile in patients completing 12 months´ of treatment similar to that seen in the placebo-controlled study.
- The beneficial effects on both bone and cartilage measures as well as symptom measures that were seen in the placebo-controlled study were maintained during the second 6-month treatment period, although results must be interpreted with caution as this was an uncontrolled extension study with a limited number of patients.
- Based on these results, progression of MIV-711 into pivotal studies as a DMOAD is therefore warranted.

Medivir AB is the Sponsor of the study, contact person *karin.gohlin@medivir.com*